J Gastrointest Canc
DOI 10.1007/s12029-013-9550-2

ORIGINAL RESEARCH

Prognostic Value of Tumor-Infiltrating Mast Cells in Outcome of Patients with Esophagus Squamous Cell Carcinoma

Ashraf Fakhrjou · Seid Mahdi Niroumand-Oscoei · Mohamad Hosein Somi · Morteza Ghojazadeh · Shahnaz Naghashi · Shabnam Samankan

Abstract
Background Squamous cell carcinoma (SCC) of the esophagus is one of the most common malignancies of the gastrointestinal tract and carries poor prognosis. The role of mast cell density (MCD) in the prognosis of most human tumors is partly known, and there is a growing body of studies addressing it. However, the prognostic value of MCD has not been investigated in esophageal SCC, and thus, it was the subject during this study.
Methods In this study, 78 patients with esophageal SCC in pT = 3 were selected, their MCD was evaluated with toluidine blue staining, and the relationship with survival rate was analyzed. Patients were compared in identical groups of lymph node involvement and post-surgery complementary therapy.
Results Survival rate was significantly decreased in patients with high MCD based on Kaplan–Meier analysis ($P < 0.001$). This relationship was also found in groups with similar lymph node involvement and post-surgery therapies.
Conclusions The results of the current study showed that high MCD in the invasive edge of tumor is related to tumor progression and decreased survival rate following surgery.

Keywords Esophagus · Squamous cell carcinoma · Mast cell · Prognosis

Introduction

Esophagus cancer is the eighth common cancer in the world and the sixth common cancer leading to death. It is primarily divided into two subtypes, squamous cell carcinoma (SCC) and adenocarcinoma. SCC composes approximately 90–95 % of all esophageal cancer worldwide and arises from the cells that line the upper part of the esophagus [1, 2].

The prognosis of esophageal cancer is extremely poor because most patients present with an advanced stage of the disease. Once presenting with a first symptom like dysphagia, the cancer has already highly progressed. The overall five-year survival rate is approximately 15 %; most patients die within the first year of diagnosis [3]. Individualized prognosis depends largely on the stage of the disease. Patients with cancer restricted entirely to the esophageal mucosa have about an 80 % five-year survival rate, but submucosal involvement brings this rate down to less than 50 %. Extension into the muscularis propria (the muscular layer of the esophagus) yields a 20 % five-year survival rate, and extension to the structures adjacent to the esophagus results in a 7 % five-year survival rate. Patients with distant metastases have a less than 3 % five-year survival rate [4–6].

Development of esophagus cancer proceeds through isolated molecular genetic changes which are acquired from the loss of genomic integrity due to continuous exposure to risk factors [7]. One of these risk factors (or better described as a protective factor) is the immune system, which is the main barrier in confronting cancerous cells, but sometimes, the immune system itself results in cancer development and exacerbation [8–10]. Mast cells are considered part of the immune system; they are resident cells in several types of tissues and contain many granules rich in histamine and heparin. Although best known for their role in allergy and anaphylaxis, mast cells play an important protective role as well, being intimately involved in wound healing and defense against pathogens [11]. During one of Paul Ehrlich's pathologic studies, the author noticed that mast cells are present in tumors' tissues at a higher than normal level, especially in carcinomas. Also, his colleagues noticed that most of the mast cells are centered in the tumor's edges. The following research showed that mast cells are present in higher numbers in basal cell carcinoma, melanoma, neurofibromatosis, and Hodgkin's

A. Fakhrjou · S. M. Niroumand-Oscoei · M. H. Somi · M. Ghojazadeh · S. Naghashi
Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

S. Samankan (✉)
Department of Pathology, Imam Reza Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
e-mail: shabnam212@ymail.com

Published online: 03 October 2013

lymphoma. Other researchers' results have shown that increased number of mast cells in multiple myeloma and Hodgkin's lymphoma carries a poor prognosis [12]. Further studies showed that there is an inverse relationship between mast cells and prognosis in some tumors. This could be explained by inflammation or another body reaction against the tumor. However, it is generally revealed that mast cells could be tumor regulators and are potential targets for adjuvant therapy for some, but not all, tumors [13].

A study which examined viability of mast cell accumulation around prostate cancer as a prognostic factor concluded that mast cell count correlates with clinical stage. In this study, the mast cell count around the cancer foci in patients with higher Gleason scores was higher than in those with low Gleason scores [14]. In another study, the mast cells and their mediators' role in human thyroid cancer were investigated. The study concluded that recruited mast cells in thyroid carcinomas promote proliferation and invasiveness of cancer cells [15].

Based on the previous reports about the role of mast cells in tumor prognosis and the lack of reports about SCC of the esophagus, this research aimed to study the relationship between MSD localized in a tumor's invasive edge and patients' prognosis.

Material and Methods

Study Design and Population

In this descriptive-analytical (survival analysis) study, we initially considered 238 patients suffering from esophageal SCC who underwent total esophagectomy operation in the Imam Reza research and clinical training center between 2005 and 2009.

In order to consider patients' staging role in their prognosis, they were categorized by the TNM method which is the most common method of staging for esophageal cancer. This method is based on guidelines created by the American Joint Committee on Cancer (AJCC) in 2010 [16]. Inclusion criteria were patients whose tumor level was in pT = 3. Patients with this criterion were divided into two groups of those with and without lymph node involvement. Patients were also categorized based on the stage of cancer and the grade of cancerous cells.

Exclusion criteria were:

- Unavailability of patients' phone number for follow-up calls to acquire information about his/her current condition and complete the study's questionnaire
- Patients' death due to surgical complications or side effects during hospitalization
- Patients' death due to any malady other than the effects of esophageal cancer (e.g., renal failure)
- Pre-operative chemotherapy (since it causes histological changes and prevents the evaluation of real mast cell density (MCD))
- Pre-operative radiotherapy
- Unavailability of patients' pathological lams and paraffin blocks (unavailability in the Pathology wing archive)
- Patients' tumor at any level other than pT = 3

Given the exclusion criteria, the questionnaire could be completed for 78 patients. The information below was extracted for all individuals using data available at the archive of the Gastroenterology Research Center, patients' hospitalization records, and follow-up phone calls. Information about cancer stage and grade was acquired from pathology reports available through patients' pathology samples and also special toluidine blue (TB) straining.

The acquired information on the patients consisted of age, sex, tissue MCD, tumor differentiation, perineural invasion, tumor vascular invasion, biggest size of the tumor, family history, post-operative, smoking, alcohol consumption, hot tea drinking habits, post-operative chemotherapy, post-operative radiotherapy, and status being dead or alive. Some of the mentioned parameters were collected as secondary parameters for probable desirable statistical analysis. To determine MCD as in similar research, counting was conducted at the invasive edge of tumors.

Histopathological Studies

Tumor specimens were fixed in 10 % buffered formalin and embedded in paraffin. Histological grading was performed on hematoxylin–eosin-stained sections. The histochemical staining of mast cells was performed with TB using the standard histochemical method. Slides were incubated with 0.1 % TB for 3 min and then rinsed with distillated water [17]. To determine MCD, a ×40 microscope lens was used and counting was conducted at 10 microscopic fields at the invasive edge of the tumor, each one equivalent to 1 mm^2. Since the scopes of different microscopes are different, to resolve this error, all counting was done using the same microscope. Counting was conducted by two investigators, including a supervisor professor (A. F.) and a correspondent assistant (S. M. N.). The mean of the counts was considered as the MCD for each patient.

Patients were divided into three groups: those with MCD below 30, between 30 and 60, and above 60. For tumor size, patients' pathology report was used and the largest diameter was recorded in the checklist.

Ethical Considerations

This study was conducted on histopathological lams and paraffin block samples archived in the Pathology ward, and

the findings were not associated with patients' therapeutic approach or medical care. Despite this fact, oral and informed consent for this study was obtained, respectively, from family of patients who had passed away and from all patients who were alive. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUMS), which was in compliance with Helsinki Declaration.

Statistical Analysis

Data obtained from the study were analyzed using descriptive statistical methods (distribution-percentage and mean ± standard deviation) and mean difference tests and a chi-square test. The Kolmogorov–Smirnov test was used to check normality of distributions. Evaluation of patients' survival rate and factors affecting it was done through a Kaplan–Meier diagram and the Cox regression model using SPSS software package version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). A P-value less than 0.05 was considered statistically significant in all steps.

Results

Demographic information of patients and also tumor-related information are shown in Table 1. The MCD of the invasive edge of the tumor is also shown in Fig. 1. The mean MCD in the invasive edge of the tumors was 44.6±25.5/cm.

Table 1 Patients' demographic and tumors' grade-related information

Variables	Item	Studied patients N (%)
Age (years)	Mean	62.8±10.3
	Min	32
	Max	88
Sex	Male	40 (51.3)
	Female	38 (48.7)
Habits	Smoking	31 (39.7)
	Drinking hot tea	29 (37.2)
Past medical history	Esophagus cancer	11 (14.1)
	Chemotherapy after operation	24 (30.8)
	Radiotherapy after operation	21 (26.9)
Tumor size (cm)	Mean ± SD	4.1±1.7
	Min	0.5
	Max	10
Differentiation status	Well-differentiated	64 (82.1)
	Moderately differentiated	9 (11.5)
	Poorly differentiated	5 (6.4)
Node involvement	Topical node involvement	45 (57.7)
	No involvement	33 (42.3)
Invasion status	Vascular invasion	38 (48.7)
	Neural invasion	40 (51.3)

The mean survival rate for all patients was 14.66± 9.64 months. The mean survival rates for patients with and without lymph node involvement were 13.2 and 17.2 months, respectively, which was not statistically significant (P=0.23). Seventy patients (89.7 %) died before January 2011 and 8 (10.3 %) were alive. Survival rate analysis of males and females showed no significant statistical difference in a Kaplan–Meier diagram (P=0.22).

In investigating the relationship of tissue MCD and survival rate, 27 persons had MCD below 30, 28 persons had MCD between 30 and 60, and the remaining 23 persons had MCD above 60. Kaplan–Meier analysis showed that the group with higher MCD has a lower survival rate (P<0.001).

The relationship between MCD with post-operative survival rate with the presence of lymph node involvement was also statistically significant. In a non-parametric comparison between MCD and tumor size using the Spearman method, no significant relationship was observed (P=0.56). There was no significant relationship between MCD and tumor differentiation using the ANOVA method (P=0.24). There was no significant relationship between tissue MCD and, respectively, lymph node involvement, vascular invasion, and neural invasion using the t-test method (P=0.70, P=0.11, and P=0.15).

Results of the Cox regression showed that among variables of patient's sex, MCD, receiving post-operative complementary therapy, neural invasion, and lymph node involvement, only variables of MCD with P<0.001 and post-operative complementary therapy are statistically significant and have correlation with survival. Patient's distributions with different MCDs in both receiving post-operative complementary therapy and without receiving post-operative complementary therapy are shown in Table 2. Patients were designated in both

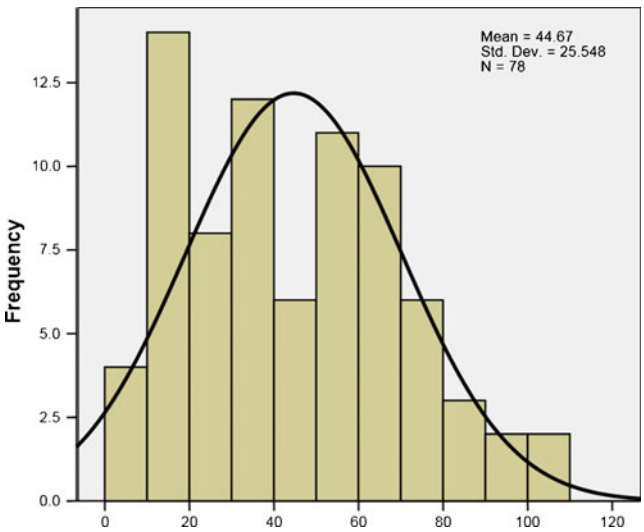

Fig. 1 MCD in the invasive edge of tumors

Table 2 Patient's distribution after operation (with or without post-operative complementary therapy groups) and their survival

Mast cell density	With post-operative complementary therapy (count of survived patients)	Without post-operative complementary therapy (count of survived patients)
Less than 30	13	14
	(2)	(5)
Between 30 and 60	9	19
	(1)	(0)
More than 60	4	19
	(0)	(0)

with or without receiving post-operative complementary therapy according to their condition which was considered by physicians. Kaplan–Meier survival analysis based on MCD is shown in Fig. 2: (a) this figure of Kaplan–Meier survival analysis of all patients (78 patients) shows that patients with MCD less than 30 had the best survival and patients with MCD more than 60 had the worst survival (which was zero) without considering patient distribution in post-operative complementary therapy, (b) this figure of Kaplan–Meier survival analysis of patients who had not undergone post-operative complementary therapy shows that patients with MCD less than 30 had the best survival while patient's survival with MCD more than 30 was zero, and (c) this figure of Kaplan–Meier survival analysis of patients who had undergone post-operative complementary therapy shows that patient's survival with MCD between 30 and 60 is higher in comparison to patients with MCD between 30 and 60 without post-operative complementary therapy; meanwhile, patients survival with MCD less than 60 is the best.

Relative risk for MCD was 1.04 (95 % CI (1.03–1.05)) and for post-operative complementary treatment 0.53 (95 % CI (0.35–0.93)). Results were also statistically significant when evaluating post-operative therapy (such as chemotherapy and radiotherapy) or no post-operative therapy ($P < 0.001$).

Discussion

Based on the present study's findings, increased tissue MCD appears to be associated with decreased survival rate in patients with esophageal SCC. This is in accordance with other similar studies carried out on other types of tumors. This relationship could be a result of the secretion of various mediators by mast cells which cause angiogenesis, damage healthy tissues, and facilitate tumor expansion.

In addition, the results of the Cox regression test showed a significant relationship between tissue MCD at the tumor's invasive edge and patients' survival rate and moreover demonstrated patients' increased survival rate with post-operative complementary therapy.

This study did not show any relationship between degree of tumor differentiation and MCD. Since differentiations are mainly related to mutations that happen before tissue infiltration with mast cells, this finding would be expected. Also, we did not find a significant relationship between MCD and tumor size, and this was also not observed in similar studies of other kind of tumors like kidney tumors [18]. This could be explained by the fact that such tumors release angiogenesis factors themselves. In a study of association between mast cells and tumor angiogenesis in esophageal SCC, a direct correlation between the number of mast cells and the tumor angiogenesis was shown in patients with esophageal SCC [19]. In another study by Coussens et al. [20] about the inflammatory role of mast cells in the up-regulation of angiogenesis during squamous epithelial carcinogenesis, it was concluded that mechanisms like release of pro-angiogenic proteases are responsible for switching inflammation to angiogenesis in mast cells.

However, this relationship is reported inversely in some tumors like breast cancer, which might be due to the different kind of mast cells infiltrating the different tumors [21]. Mast cell infiltration in prostate cancer is also reported as an independent prognostic factor and implies poor prognosis [14]. Many studies have shown that high MCD in colorectal cancer

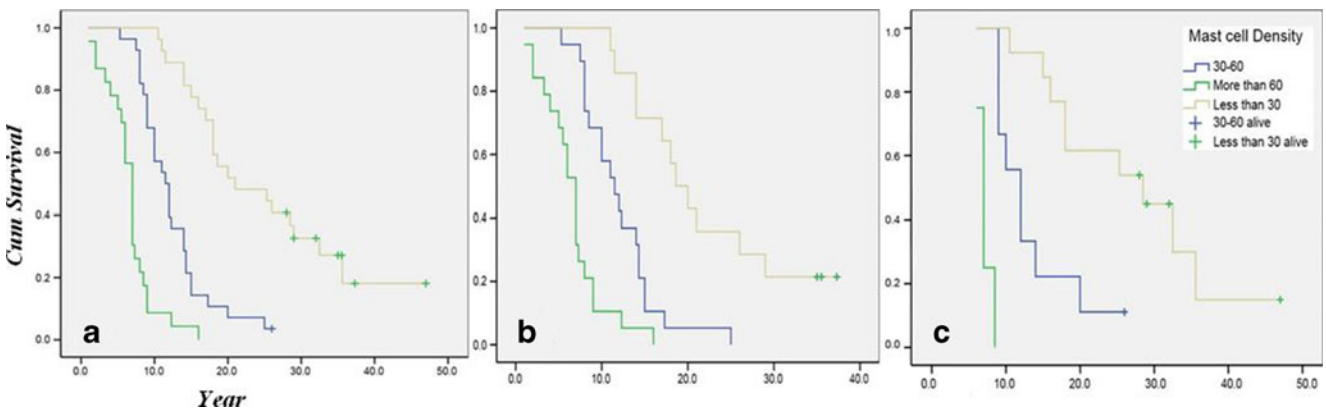

Fig. 2 Kaplan–Meier survival analysis based on MCD

is a malignant sign for prognosis [22–24]. Such correlation has been shown in lung [25], pancreas [26], and hepatocellular [27] cancers. It has also been shown that reducing the number of mast cells by genetic or pharmaceutical methods increases apoptosis in colon polyposis [28]. In the most relevant study by Elpek et al. on 53 patients, they found a significant relationship between MCD and poor prognosis in esophageal SCC [29].

Angiogenesis is a prognostic factor in most types of tumors. The process is a complicated event depending on angiogenic factors released from tumor cells or host immune cells. Among the body immune cells, mast cells usually have an important role in tumor progression by secreting angiogenic factors. The existence of mast cells, angiogenesis level, and disease development in body tumors such as melanoma and other gastrointestinal tumors like colon have been investigated by multiple studies, and a significant relationship has been shown [19, 30]. Basic fibroblast growth factor, interleukin 4 (IL-4), IL-8, and tumor necrosis factor α (TNF-α) are among the mediators present in mast cell granules and strongly induce angiogenesis [31, 32].

It had been reported that tumor angiogenesis in esophageal SCC is closely related to overall patient survival, and antiangiogenic agents have been emphasized as potential therapeutic agents [33–35]. The mast cell heparin inhibitors, protamine and platelet factor 4, have been reported as angiogenesis inhibitors and are probable new treatment options for esophageal SCC [36, 37].

High levels of mast cells imply poor prognosis even in follicular lymphoma treated by immunotherapy [38]. In Hodgkin's lymphoma, an increase in mast cells indicates poor prognosis, and this effect is probably independent of the angiogenesis effect of mast cells and affects CD30+ Reed–Sternberg cells [39]. Mast cells have an etiologic relationship with creating neurofibromas in people with neurofibromatosis type 1 [40]. Crivellato et al. showed that tumor progression depends on angiogenesis mediators of mast cells, as well as chemostasis of macrophage, neutrophil, and eosinophil [41].

There are also some conflicting reports about the role of mast cells in cancer prevention. One study of mast cell invasion to tumor cell islets concluded that a high number of cells were accompanied by a higher survival rate in non-small cell lung cancer [42]. Another study demonstrated that high MCD is associated with favorable prognosis in breast cancer [43]. Kankkunen et al. 's study about the analysis of tryptase- and chymase-containing mast cells in benign and malignant breast lesions showed better survival in lesions with high MCD [44]. Interestingly, Johansson et al. looked differently at the role of mast cells in prostate cancer. They reported that mast cells inside the tumor prevent angiogenesis, while mast cells around the tumor increase angiogenesis [45].

Conclusion

Generally, it is possible to state that inflammation has a basic role in tumor development, and given the presence of mast cells in SCC and their ability to secrete a wide range of materials, mast cells have an important role in the development of SCC. Considering the issues above, it is possible to use medications which target mast cells in cases in which mast cells' functions are related to the prognosis. This fact points to the need for more studies on the distribution of mast cells in different tumors.

Acknowledgments This study was supported by the Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Also, the present paper was part of a research thesis carried out in the Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences. The authors would like to thank Mohammad Naghavi-Behzad (Student Research Committee, Tabriz University of Medical Sciences), Laura Vail (Health Sciences Informatics, Johns Hopkins School of Medicine), and Dr. Nariman Nezami (Johns Hopkins Hospital) for their kind help.

Conflict of Interest The authors declare that they have no competing interests in any aspect of this study. There is no commercial association, either directly or through immediate family, in such areas as expert testimony, consulting, honoraria, stock holdings, equity interest, ownership, patent-licensing situations, or employment. There are also no conflicts for personal relationships and academic competition. No one was paid in preparing this manuscript.

References

1. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349(23):2241–52. Epub 2003/12/06.
2. Stewart BW, Kleihues P. World cancer report. Lyon: IARC press; 2003.
3. Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. Int J Cancer J Int du Cancer. 2003;105(1):98–100. Epub 2003/04/03.
4. Steevens J, Botterweck AA, Dirx MJ, van den Brandt PA, Schouten LJ. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol. 2010;22(6):669.
5. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.
6. Ghojazadeh M, Mohammadi M, Azami-Aghdash S, Sadighi A, Piri R, Naghavi-Behzad M. Estimation of cancer cases using capture–recapture method in Northwest Iran. Asian Pac J Cancer Prev APJCP. 2013;14(5):3237–41. Epub 2013/06/28.
7. Brennan JA, Mao L, Hruban RH, Boyle JO, Eby YJ, Koch WM, et al. Molecular assessment of histopathological staging in squamous-cell carcinoma of the head and neck. N Engl J Med. 1995;332(7):429–35.
8. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer. 2006;6(1):24–37.
9. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Sci Signal. 2011;331(6024):1565.
10. Ghojazadeh M, Azar ZF, Saleh P, Naghavi-Behzad M, Azar NG. Knowledge and attitude of Iranian university students toward human

papilloma virus. Asian Pac J Cancer Prev APJCP. 2012;13(12):6115–9. Epub 2012/01/01.
11. Prussin C, Metcalfe DD. 4. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immun. 2003;111(2 Suppl):S486–94. Epub 2003/02/20.
12. Beaven MA. Our perception of the mast cell from Paul Ehrlich to now. Eur J Immunol. 2009;39(1):11–25. Epub 2009/01/09.
13. Nechushtan H. The complexity of the complicity of mast cells in cancer. Int J Biochem Cell Biol. 2010;42(5):551–4. Epub 2009/12/23.
14. Nonomura N, Takayama H, Nishimura K, Oka D, Nakai Y, Shiba M, et al. Decreased number of mast cells infiltrating into needle biopsy specimens leads to a better prognosis of prostate cancer. Br J Cancer. 2007;97(7):952–6. Epub 2007/09/13.
15. Melillo RM, Guarino V, Avilla E, Galdiero MR, Liotti F, Prevete N, et al. Mast cells have a protumorigenic role in human thyroid cancer. Oncogene. 2010;29(47):6203–15. Epub 2010/08/24.
16. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471–4.
17. Strobel S, Miller H, Ferguson A. Human intestinal mucosal mast cells: evaluation of fixation and staining techniques. J Clin Pathol. 1981;34(8):851–8.
18. Mohseni MG, Mohammadi A, Heshmat AS, Kosari F, Meysamie AP. The lack of correlation between mast cells and microvessel density with pathologic feature of renal cell carcinoma. Int Urol Nephrol. 2010;42(1):109–12.
19. Tomita M, Matsuzaki Y, Edagawa M, Shimizu T, Hara M, Sekiya R, et al. Association of mast cells with tumor angiogenesis in esophageal squamous cell carcinoma. Dis Esophagus Off J Int Soc Dis Esophagus ISDE. 2001;14(2):135–8. Epub 2001/09/13.
20. Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, et al. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev. 1999;13(11):1382–97.
21. Oldford SA, Haidl ID, Howatt MA, Leiva CA, Johnston B, Marshall JS. A critical role for mast cells and mast cell-derived IL-6 in TLR2-mediated inhibition of tumor growth. J Immunol. 2010;185(11):7067–76.
22. Acikalin MF, Oner U, Topcu I, Yasar B, Kiper H, Colak E. Tumour angiogenesis and mast cell density in the prognostic assessment of colorectal carcinomas. Dig Liver Dis Off J Italian Soc Gastroenterol Italian Assoc Study Liver. 2005;37(3):162–9. Epub 2005/05/13.
23. Gulubova M, Vlaykova T. Prognostic significance of mast cell number and microvascular density for the survival of patients with primary colorectal cancer. J Gastroenterol Hepatol. 2009;24(7):1265–75. Epub 2007/07/25.
24. Yodavudh S, Tangjitgamol S, Puangsa-art S. Prognostic significance of microvessel density and mast cell density for the survival of Thai patients with primary colorectal cancer. J Med Assoc Thailand Chotmaihet Thangphaet. 2008;91(5):723–32.
25. Imada A, Shijubo N, Kojima H, Abe S. Mast cells correlate with angiogenesis and poor outcome in stage I lung adenocarcinoma. Eur Respir J Off J Eur Soc Clin Respir Physiol. 2000;15(6):1087–93. Epub 2000/07/08.
26. Khazaie K, Blatner NR, Khan MW, Gounari F, Gounaris E, Dennis K, et al. The significant role of mast cells in cancer. Cancer Metastasis Rev. 2011;30(1):45–60. Epub 2011/02/03.
27. Ju MJ, Qiu SJ, Gao Q, Fan J, Cai MY, Li YW, et al. Combination of peritumoral mast cells and T-regulatory cells predicts prognosis of hepatocellular carcinoma. Cancer Sci. 2009;100(7):1267–74. Epub 2009/05/13.
28. Gounaris E, Erdman SE, Restaino C, Gurish MF, Friend DS, Gounari F, et al. Mast cells are an essential hematopoietic component for polyp development. Proc Natl Acad Sci. 2007;104(50):19977–82.
29. Elpek GO, Gelen T, Aksoy NH, Erdogan A, Dertsiz L, Demircan A, et al. The prognostic relevance of angiogenesis and mast cells in squamous cell carcinoma of the oesophagus. J Clin Pathol. 2001;54(12):940–4. Epub 2001/12/01.
30. Galinsky DS, Nechushtan H. Mast cells and cancer—no longer just basic science. Crit Rev Oncol Hematol. 2008;68(2):115–30. Epub 2008/07/18.
31. Reed JA, Albino AP, McNutt NS. Human cutaneous mast cells express basic fibroblast growth factor. Lab Investig J Tech Methods Pathol. 1995;72(2):215–22. Epub 1995/02/01.
32. Nilsson G, Svensson V, Nilsson K. Constitutive and inducible cytokine mRNA expression in the human mast cell line HMC-1. Scand J Immunol. 1995;42(1):76–81. Epub 1995/07/01.
33. Takebayashi Y, Natugoe S, Baba M, Fukumoto T, Takao S, Akiba S, et al. Angiogenesis in esophageal squamous cell carcinoma. Oncol Rep. 1998;5(2):401–4. Epub 1998/04/18.
34. Tanigawa N, Matsumura M, Amaya H, Kitaoka A, Shimomatsuya T, Lu C, et al. Tumor vascularity correlates with the prognosis of patients with esophageal squamous cell carcinoma. Cancer. 1997;79(2):220–5. Epub 1997/01/15.
35. Chen L, Luo G, Tan Y, Wei J, Wu C, Zheng L, et al. Immunolocalisation of tissue factor in esophageal cancer is correlated with intratumoral angiogenesis and prognosis of the patient. Acta Histochem. 2010;112(3):233–9.
36. Wang Q, Lei X, Zhu S, Zhang S. Angiotensin–I converting enzyme inhibitors suppress angiogenesis and growth of esophageal carcinoma xenografts. Dis Esophagus. 2012;25(8):757–63.
37. Amirnia M, Babaie-Ghazani A, Fakhrjou A, Khodaeiani E, Alikhah H, Naghavi-Behzad M, et al. Immunohistochemical study of cyclooxygenase-2 in skin tumors. J Dermatol Treat. 2012. Epub 2012/06/07.
38. Taskinen M, Karjalainen-Lindsberg ML, Leppa S. Prognostic influence of tumor-infiltrating mast cells in patients with follicular lymphoma treated with rituximab and CHOP. Blood. 2008;111(9):4664–7. Epub 2008/03/01.
39. Molin D, Edstrom A, Glimelius I, Glimelius B, Nilsson G, Sundstrom C, et al. Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. Br J Haematol. 2002;119(1):122–4. Epub 2002/10/03.
40. Yang FC, Chen S, Clegg T, Li X, Morgan T, Estwick SA, et al. Nf1+/- mast cells induce neurofibroma like phenotypes through secreted TGF-beta signaling. Hum Mol Genet. 2006;15(16):2421–37. Epub 2006/07/13.
41. Crivellato E, Nico B, Ribatti D. Mast cells and tumour angiogenesis: new insight from experimental carcinogenesis. Cancer Lett. 2008;269(1):1–6. Epub 2008/05/03.
42. Welsh TJ, Green RH, Richardson D, Waller DA, O'Byrne KJ, Bradding P. Macrophage and mast-cell invasion of tumor cell islets confers a marked survival advantage in non-small-cell lung cancer. J Clin Oncol. 2005;23(35):8959–67.
43. Rajput AB, Turbin DA, Cheang MC, Voduc DK, Leung S, Gelmon KA, et al. Stromal mast cells in invasive breast cancer are a marker of favourable prognosis: a study of 4,444 cases. Breast Cancer Res Treat. 2008;107(2):249–57. Epub 2007/04/14.
44. Kankkunen JP, Harvima IT, Naukkarinen A. Quantitative analysis of tryptase and chymase containing mast cells in benign and malignant breast lesions. Int J Cancer J Int du Cancer. 1997;72(3):385–8. Epub 1997/07/29.
45. Johansson A, Rudolfsson S, Hammarsten P, Halin S, Pietras K, Jones J, et al. Mast cells are novel independent prognostic markers in prostate cancer and represent a target for therapy. Am J Pathol. 2010;177(2):1031–41. Epub 2010/07/10.